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Randomized controlled pilot trial of naloxone-on-release to prevent post-prison opioid overdose deaths

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RUNNING HEAD: N-ALIVE to prevent opioid deaths post-release

CONFLICTS of INTEREST

MKBP, LC, AMM: no conflicts of interest.

JS: JS is a researcher and clinician who has worked with a range of types of treatment and rehabilitation service-providers, including treatments within prison and on prison release. JS is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London. He has also worked with a range of governmental and non-governmental organisations, and with pharmaceutical companies to seek to identify new or improved treatments (including naloxone

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products) from whom he and his employer (King's College London) have received honoraria, travel costs and/or consultancy payments. This includes work with, during past 3 years, Martindale, Reckitt-Benckiser/Indivior, MundiPharma, Braeburn/MedPace and trial medication supply from iGen. His employer (King's College London) has registered intellectual property on a novel buccal naloxone formulation with which JS is involved. JS has also been named in a patent registration by a Pharma company as inventor of a concentrated nasal naloxone spray. For a fuller account, see JS's web-page at <http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx>.

SMB: SMB served on Scotland's National Naloxone Advisory Group and co-authored the peer-review paper on before/after evaluation at 3-years of Scotland's National Naloxone Policy. SMB holds GlaxoSmithKline shares.

N-ALIVE pilot TRIAL's CLINICAL TRIAL REGISTRATION: ISRCTN34044390

Randomized controlled pilot trial of naloxone-on-release to prevent post-prison opioid overdose deaths

ABSTRACT

Background and aims: Naloxone is an opioid antagonist used for emergency resuscitation following opioid overdose. Prisoners with a history of heroin injection have a high risk of drug-related death soon after release from prison. The N-ALIVE pilot trial (ISRCTN34044390) tested feasibility measures for randomized provision of naloxone-on-release (NOR) to eligible prisoners in England.

Design: Parallel group randomized controlled pilot trial.

Setting: English prisons.

Participants: A total of 1685 adult heroin injectors, incarcerated for at least 7 days pre-randomization, release due within 3 months and more than 6 months since previous N-ALIVE release.

Intervention: Using 1:1 minimization, prisoners were randomized to receive on-release a pack containing either a single 'rescue' injection of naloxone or a control pack with no syringe.

Measurements: Key feasibility outcomes were tested against prior expectations: on participation (14 English prisons; 2800 prisoners), consent (75% for randomization), returned prisoner self-questionnaires (RPSQs: 207), NOR-carriage (75% in first 4-weeks) and overdose-presence (80%).

Findings: Prisons (16) and prisoners (1685) were willing to participate (consent-rate, 95% CI: 70% to 74%); 218 RPSQs were received; NOR-carriage (95% CI: 63% to 79%) and overdose-presence (95% CI: 75% to 84%) were as expected. We randomized 842 to NOR, 843 to control during 30 months but stopped early because only one third of NOR administrations was to the ex-prisoner. Nine deaths within 12 weeks of release were registered for 1557 randomized participants released before 9 December 2014.

Conclusions: Large randomized trials are feasible with prison populations. Provision of take-home emergency naloxone prior to prison release may be a life-saving interim measures to prevent heroin overdose deaths among ex-prisoners and the wider population.

Randomized controlled pilot trial of naloxone-on-release to prevent post-prison opioid overdose deaths

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INTRODUCTION

Prisoners with a history of heroin injection have a high risk of drug-related death (DRD) soon after prison-release which was estimated at 5 DRDs per 1000 eligible releases on the basis of record-linkage studies in Scotland in 1996-99¹, and in England and Wales in 1999-2002.² See also meta-analyses^{3,4}.

Naloxone is an opioid antagonist that can be administered intramuscularly and is used by emergency services to reverse heroin/opioid overdose⁵. The feasibility of randomized provision of naloxone-on-release (NOR) to a high-DRD-risk population, such as inmates with a history of heroin injection use on their release from prison as proposed by Bird and Hutchinson¹, had not been investigated. Prison-based randomized trials must address *either* a concern that applies specifically to prisoners (as here) - to counter the challenge that the same trial could equally well have been conducted in the outside community; *or* be able to point to parallel trials on the outside to answer the challenge of exploiting prisoners' captivity.

One recent international review of non-randomized community initiatives on take-home naloxone, mainly in USA and UK, with follow-up for 3 to 6 months of their trainees, gave an estimated fatality-rate at witnessed opioid overdose of 6% (upper 95% confidence limit: 11%), suggesting that a target for the annual distribution of naloxone-kits should be 9 to 20 times a nation's annual number of opioid-related deaths⁶. A recent comprehensive monograph⁷ has documented the historical development (from the 1990s) and spread of take-home naloxone programmes through North America, Europe and Australia; and considered their practical implementation, including the training of naloxone recipients in how to recognise and respond to an overdose. Although supported by the World Health Organization⁸, barriers remain to accessing take-home naloxone: in most European jurisdictions, naloxone is a prescription-only medicine; in others (see below), its addition to the exempt list of prescription-only medicines did little to change clinical practice, take-home naloxone being deemed contentious⁹ by some, complex¹⁰ by others. When the notification of overdose events triggers a report to the police, this may discourage witnesses from contacting emergency medical services; and the need to inject naloxone can prove a psychological barrier for some responders as well as being a potential health risk for all who administer the injection⁷.

In 2005, naloxone was added to UK's exempt list of prescription-only medicines that can be administered by anyone to save life in an emergency.¹¹ Bird, Parmar and Strang then applied to the UK Medical Research Council (MRC) for funding to conduct a randomized effectiveness study of NOR for prisoners with a history of heroin use by injection. The definitive **NALoxone InVEstigation** (N-ALIVE) trial was to investigate if NOR could reduce DRDs in the first 4 weeks after release by 30% and in weeks 5-12 by 20%. In 2008, MRC funded the N-ALIVE pilot trial to randomize the first tenth of 56,000 prisoners needed for the main trial: half in Scotland, the other half in 15 prisons in England and Wales. The rationale for the N-ALIVE trial has been previously described¹².

In January 2011, Scotland became the first nation to make both community-based take-home naloxone and NOR for eligible prisoners a funded public health policy.^{6 13-15} Wales followed suit later in 2011.¹⁶ Accordingly, N-ALIVE was conducted in English prisons only, and its target accrual reduced to 2,800 participants.

Our *a priori* estimation of the likely effectiveness of naloxone¹ accounted for some-one else being present four-fifths of opiate overdoses¹²; and that, most often, the others present (peers or family-members) were willing to intervene but lacked effective means¹⁷.

We report the key feasibility outcomes of the N-ALIVE pilot trial compared with prior expectations in the trial protocol (ISRCTN34044390)¹⁸, as follows:

- i) Participation by prisons and prisoners;
- ii) Consents for randomization, Returned Prisoner Self-Questionnaire (RPSQ), phone-contact sub-study;
- iii) Receipt of RPSQs;
- iv) NOR-carriage and overdose-presence;
- v) Whether the N-ALIVE main trial could go ahead as planned, including assessment of to whom NOR was administered.

METHODS

Design: plausible effectiveness and main trial size, plus key assumptions to be checked by pilot trial

N-ALIVE was a randomized controlled trial of parallel groups (see **Figure 1**). Research-trained prison-based N-ALIVE workers recruited and consented eligible prisoners.

The N-ALIVE main trial was to investigate if NOR could reduce DRDs in the first 4 weeks after release by 30%, from 140 to 98 per 28,000 eligible releases; and in weeks 5-12 by 20%, from 35 to 28 per 28,000 eligible releases, for which randomization of 56,000 eligible releases would be needed for 80% power at 5% significance level. In 2008, MRC funded the N-ALIVE pilot trial to randomize the first tenth of 56,000 prisoners needed for the main trial: half in Scotland, the other half in prisons in England and Wales.

Our *a priori* estimation of NOR's likely effectiveness in the main trial took into account that: a) someone else is present at 80% of opiate overdoses¹²; b) 75% of ex-prisoners randomized to NOR would carry NOR in the first 4-weeks, reducing to 50% in weeks 5-12, but negligible thereafter¹⁸; c) most often, the others present (peers or family-members) are willing to intervene¹⁷ but, conservatively, we assumed a 50:50 chance that present others would have the presence of mind to locate, assemble and administer NOR to the ex-prisoner¹⁸. Hence, NOR's plausible effectiveness at reducing DRDs was $80\% \times 75\% \times 50\%$, or 30%, in the 1st 4-weeks, but reduced to 20% in weeks 5-12.

In Scotland and in England and Wales, the N-ALIVE pilot trial was to test our key assumptions on i) participation, ii) consents, iii) receipt of RPSQs, iv) NOR-carriage and overdose presence, and hence v) whether the N-ALIVE main trial could go ahead as planned, including by assessment of to whom NOR was administered.

Because the N-ALIVE pilot trial could randomize in English prisons only, its target accrual reduced to 2,800 participants, sufficient for assessing i) to v) for England. Key outcome measures and prior expectations for the pilot trial¹⁸ are detailed in **Table 1**. The N-ALIVE pilot trial was approved by Essex 2 Research Ethics Committee.

Data Collection

Study forms were sent by our prison-based N-ALIVE workers to MRC Clinical Trials Unit by post or fax. Reporting of release-date was particularly important as marking the start of a participant's at-risk period. Screening logs for eligibility were introduced in September 2012.

The randomization form checked a potential participant's eligibility and consents and provided the information needed for minimization (see below). Other forms recorded the participant's release-date or date of prison-transfer. Information on date and cause of death within 4, 12 weeks and six months of a participant's N-ALIVE release-date was obtained from the Office for National Statistics by checking periodically against registered deaths, most recently on 21 April 2016. The RPSQ was designed to answer objectives iv) and v).

Eligibility, Randomization and Consent

Eligibility criteria were age greater than 18 years (upper limit of 44 removed 16 months into the trial because 10% of otherwise eligible prisoners were being excluded, see **Table 2**), history of heroin use by injection, incarcerated for at least 7 days, expected release date within 3 months of randomization-date, not previously randomized in N-ALIVE trial and then consent withdrawn prior to release, and written informed consent. Exclusion criteria were known history of anaphylactic reaction to naloxone, confirmed/declared pregnancy or pregnancy intended within six months, normally resident outside of UK, and randomization-date within six months of most recent N-ALIVE release-date (or, if missing, within one year of previous randomization-date).

Participants were randomized (1:1) by MRC Clinical Trials Unit to receive on release a pack containing either a single 'rescue' injection of naloxone or a control pack which did not contain naloxone – there was no placebo. Minimization (with 80:20 randomization) was applied across: gender, age-group (18-24, 25-34, 35+ years), re-randomization, management of opioid dependency at randomization (substitution, detoxification, other), and likely interval from randomization to index release (within 28 days, 4-12 weeks).

Consent for mortality follow-up was mandatory at the time of consent for randomization, but could be withdrawn while participants were still in prison: in such a case, the participant would be withdrawn from the trial and no attempt would be made to provide a pack on release. Additionally, prisoners were asked for their consent for i) record-linkage to establish if participants had had any admissions to accident and emergency departments for non-fatal overdose in the 12 weeks following their N-ALIVE release-date; and ii) randomization in a once-only phone-contact sub-study¹⁸, see **Figure 1** and **Supplementary**.

The trial was double-blind prior to release so that, while the participant was still in custody and pre-release, neither the participant nor prison-based N-ALIVE staff nor prison staff knew the allocation. Participants learned their allocation when they opened the pack at the time of their release.

N-ALIVE packs

Each prison had a supply of pre-numbered sealed N-ALIVE packs¹⁹. Control and naloxone packs were identical in appearance, sounded alike when shaken, and were similar weights. All packs contained the N-ALIVE DVD, a wallet and had tamper-evident stickers attached.

The wallet in the control pack did not contain a syringe. The wallet in the naloxone pack included all the same material as the control wallet but also contained a pre-filled syringe, the unscrewed plunger rod for the syringe and a safety-covered, sterile-packed hypodermic needle, see **Supplementary**. The plunger had been removed from the syringe barrel so that both fitted into the N-ALIVE wallet; both had to be fitted to the syringe before use. The syringe contained 2mg of naloxone hydrochloride in 2ml of solution, for once-only intramuscular injection in the event of overdose. During information and consent sessions, participants were advised on how to administer the N-ALIVE-recommended 0.8mg intramuscular dose of naloxone. For trial purposes, the naloxone needed to be a single product¹⁹. As none of the available products fitted our needs well, the correct dose in single product form was most crucial. Accordingly, we selected the 2mg pre-loaded syringe as an acceptable formulation for the pilot trial period¹⁹; which necessitated additional instructions for administration to be limited to a 0.8mg dose.

Returned Prisoner Self-Questionnaire

We asked participants if they were willing to complete an anonymous follow-up questionnaire, if they returned to prison within six months of their most recent N-ALIVE release date. The RPSQ identified the participant's randomized assignment and the time-interval between the preceding N-ALIVE release-date and completion-date but, to encourage frankness, the identity of the respondent was not recorded. Forms were neither checked nor overseen by the N-ALIVE worker unless the respondent so chose.

Statistical Analysis

All validly randomized participants who were released from custody before 9 December 2014 are included in the analyses.

Simple summary statistics for percentages or counts (together with 95% confidence intervals, CIs) are used to assess consistency with prior expectations: on consents, RPSQs, NOR-carriage in the 1st 4-weeks, overdose presence and the use made of NOR to save the life of others than those for whom it was prescribed. Comparison of rates between NOR versus control group, based on RPSQs, is by chi-squared or Fisher's exact test, as appropriate.

Formal comparison of risk-behaviours versus perception between NOR versus control is based on a composite score for risk-behaviours, derived post-hoc from RPSQs. Early cessation of randomization in the N-ALIVE pilot trial made it unlikely that subsequent NOR-evaluations would be individually randomized. We therefore needed to make best use of the N-ALIVE pilot trial's data to explore whether those randomized to NOR had increased the riskiness of their heroin use soon after release, as distinct from how participants perceived that their behaviour had been changed by taking part in N-ALIVE.

Risk Score

To analyse how provision of NOR impacted on participants' heroin use and related risk behaviours soon after release, a risk score based on RPSQ responses was devised by SMB and AMM; and agreed by JS and MKBP (see **Supplementary** for how individual questions were scored) before being implemented by LC and tested for interaction (NOR versus control) against perceived behaviour-change.

RESULTS

Recruitment: prisons and participants

The trial was conducted in 16 prisons in England. Based on screening logs, the consent-rate for randomization among eligible prisoners was 72% (1283/1777, 95% CI: 70% to 74%), just short of our prior assumption of 75% (**Table 1**).

Between May 28th 2012 and December 8th 2014, we randomized 1685 participants (842 to NOR; 843 to control). Nine participants are considered 'not-randomized' because they were withdrawn prior to release: four withdrew consent for mortality follow-up prior to their release, while five were found to be ineligible, see **Figure 2** [CONSORT].

Consent to complete the RPSQ was given by 85% of participants (1417/1676), better than our prior expectation of 75%. Consent to take part in the phone-contact study was provided by 56% (946/1676, 95% CI: 54% to 59%) of participants, better than our prior assumption of 50%.

Re-Randomizations

Of the 129 participants randomized more than once, 61 had received naloxone on the first occasion while 68 received control, consistent with expectation (64.5 each) if prior allocation did not influence the decision to be re-randomized.

Early cessation of randomization: decisions by Trial Steering-Data Monitoring Committee (TS-DMC)

We closed the trial to accrual on 8th December 2014, ahead of our planned closure date²⁰. An unscheduled interim analysis of the feasibility outcomes of the N-ALIVE pilot trial was prompted by the release on 28th October 2014 of the 3rd year of results from Scotland's National Naloxone Programme²¹, see **Figure 3**.

When randomization to N-ALIVE stopped, all participants who remained in custody were to be offered naloxone on their release, including those due to receive a control pack. The Principal Investigators at our prisons so agreed. Participants were otherwise followed up per-protocol.

Baseline Characteristics

The baseline characteristics and treatment allocation of the 1557 randomized participants who were released by 8th December 2014 (93% of the 1676 who were eligible to receive a pack on release) are shown in **Table 2**.

Provision of Packs on Release

Of those participants released before 8th December 2014, 81% received their N-ALIVE pack on release (1266/1557; 95% CI: 79% to 83%).

RPSQs: Return-rate and Findings

We received 218/1557 (14%) RPSQs by December 8th, 2014; 205 with information on treatment assignment (112 naloxone; 93 controls), consistent with our prior expectation of 207 (95% CI: 179 to 235), see **Table 1**. Median and mean time (sd) from release-date to RPSQ-completion were 64 and 80 (62) days.

(a) naloxone carriage and administration: Of RPSQ-respondents assigned to NOR, 76% (85/112; 95% CI: 68% to 84%) told a family member or friend about their naloxone (**Table 3**) and 71% (80/112; 95% CI: 63% to 79%) reported carriage of naloxone in the first 2-weeks post-release, consistent with prior expectation (**Table 1**). Naloxone acquisition from other sources occurred at a non-differential, low rate (12/205, 95% CI: 2.6% to 9.1%). More often, RPSQ-respondents reported that their NOR had been administered to 'save' someone else (14%; 16/112) than themselves (5%; 5/112), see also **Figure 3**.

Twenty-one percent (23/112) reported administration of naloxone to themselves or another before the arrival of a doctor or ambulance versus 9% (8/93) for controls (chi-square on 1df = 5.64; $p=0.02$). Cumulative accounting for overdose victims being taken to hospital was 26% (29/112) for NOR versus 28% (26/93) for controls; chi-square on 1df = 0.11 ($p=0.74$).

(b) personal drug use, injecting and overdose events: Two-thirds of RPSQ-respondents had used heroin in the first fortnight post-release (67%, 137/205).

Half (105/205) of the RPSQ-respondents had injected in the first fortnight – 58% (65/112) for NOR and 43% (40/93) of controls; 26% (53/205; 95% CI: 20% to 32%) had injected when alone in the first 2-weeks post-release, on a mean of six days out of 14 (95% CI: 4.9 to 7.1 days), broadly consistent with our prior expectation of someone else present at 80% of opiate overdoses (**Table 3; Table 1**).

Five percent of RPSQ-respondents (10/205) had personally experienced an overdose within the first fortnight – 7% (8/112) for NOR and 2% (2/93) of controls (Fisher's exact test, $p=0.12$). Thereafter until re-imprisonment, the proportion personally overdosing was 5% (11/205) for NOR and controls alike.

(c) witnessed overdoses and actions taken: Fifteen percent of RPSQ-respondents (31/205) had personally witnessed an overdose in the first fortnight post-release – 17% (19/112) for NOR and 13% (12/93) of controls. Thereafter until re-imprisonment, the witness-proportion was 15% (30/205) for NOR and controls alike.

(d) opinions about NOR and the N-ALIVE trial: Taking part in N-ALIVE was positively associated with safer heroin use by 60/112 (54%) RPSQ-respondents randomized to NOR and 30/93 (32%) of controls (chi-square on 1df = 9.37, $p<0.002$). Suggestions made by 113 RPSQ-respondents were most

commonly: ‘everyone should get naloxone’ (22), ‘everyone should get naloxone not just 50:50’ (10); ‘availability and access’ (11); ‘safer perception’ (8), ‘education and awareness’ (8); and ‘research trial a good idea’ (6), see **Supplementary**. Fifty difficulties were cited, the top three being: ‘didn’t get naloxone’ (12), ‘no pack on release’ (7) and ‘police not aware’ (6).

Four difficulties were potential adverse events: (1) because police were unaware of the N-ALIVE pilot trial, one ex-prisoner would have been arrested but for intercession by a drug-intervention-programme worker; (2) ex-prisoner’s partner was worried about children finding his naloxone; (3) acquaintance of another ex-prisoner took the naloxone “to see if he got a buzz from it”; and (4) ex-prisoner was unsure how much of naloxone to administer to a person who had overdosed.

Risk Score

Table 4 shows that RPSQ-respondents’ mean risk score was not significantly different between NOR (3.9) and controls (3.5). We observed an interaction ($p=0.049$) between randomized assignment, self-reported safer behaviour and mean risk score: for controls, but not for NOR, RPSQ-respondents’ mean risk score was significantly lower for those who self-reported safer behaviour (2.4) versus not (4.0).

Drug-Related Deaths

Only half of the DRDs registered in England and Wales in a specific calendar year actually occur in that calendar year^{22 23} and so it was necessary to wait at least a year to report on DRDs.

Nine deaths had occurred in the 12 weeks post-release among 1557 randomized participants and were registered with the Office for National Statistics before 21 April 2016 (**Table 1** and **Supplementary**). Five were DRDs, consistent with our null-expectation of 9.7 DRDs in 12-weeks after release; but only two DRDs occurred in the 1st 4-weeks, well below our null-expectation of 7.9 (**Table 1**).

Of the four opioid-related DRDs, three were randomized to NOR of whom one was released without his pack. The participant whose DRD was not opioid-related was also randomized to NOR and had been released without his pack.

DISCUSSION

The N-ALIVE pilot trial has randomized more prisoners than any other prison-based, individually randomized controlled trial in Europe. We have shown that large-scale trials of public health interventions are feasible within prisons. Prisoners themselves showed enthusiasm for the N-ALIVE trial - their consent rate was excellent (72%).

The N-ALIVE pilot trial stopped early because its own data together with those from Scotland's National Naloxone Programme were persuasive that approximately two-thirds of NOR administrations were **not** to the ex-prisoner for whom NOR was assigned. We had no means of knowing the identities of these other persons: confounding of N-ALIVE's control group could have occurred. The N-ALIVE pilot trial ceased because individualized randomization to NOR cannot offer a clear-cut answer: other trial designs are required.

We were concerned that a 50% consent-rate combined with 50% contact-rate for the half randomized to actual phone-contact would mean that only 195 phone-interviews would be likely to be achieved from 1557 randomized participants. In practice, the achievement was lower still with 81 successful phone interviews. By contrast, RPSQs which were specifically designed to protect the respondent's confidentiality achieved their anticipated response-rate.

Other prior assumptions were vindicated by the feasibility trial. Few actual or potential adverse events were reported: one reply-card informed us that naloxone had been administered to an

overdose victim who had survived but had experienced withdrawal symptoms; one ex-prisoner had faced arrest because the police were not sufficiently aware of the N-ALIVE trial; and two respondents cited their or a partner's concern for safer packaging lest children might access the naloxone.

Notwithstanding RPSQ-respondents' eight reports of overdose in the first fortnight for NOR versus two for controls, and comparable injection rates in the first fortnight post-release (**Table 3**), RPSQ-respondents randomized to NOR self-reported safer heroin use compared with controls. However, our risk score comparisons (**Table 4**) showed a significant interaction whereby only for controls did the mean risk score align with self-reported safer behaviour. Returned prisoners randomized to NOR perceived greater safety than their RPSQ answers demonstrated, which suggests some risk compensation about which Strang et al²⁴ forewarned, see also other prevention policies from seat-belt legislation to safety helmets²⁵⁻²⁷, where a degree of risk compensation detracted in a small way from the policy's overall benefit. N-ALIVE participants' main suggestion was that naloxone should be made more widely available to all those at-risk.

To our knowledge, no previous contemporaneous before/after policy-evaluation and randomized trial of effectiveness has had the same primary outcome: here, DRDs or opioid-related DRDs with a 4-week antecedent of prison-release^{6 9 14}. The N-ALIVE team convened its TS-DMC ahead of the release of the third year results from Scotland's National Naloxone Programme.^{6 21} Consistency between RPSQ-responses on the administration of NOR (another vs self, 15:5) and Scotland's data on the utilization of NOR by those who applied for re-supply (21:12) convinced the TS-DMC that an individually-randomized main trial was infeasible because only one-third of NOR administrations was to the ex-prisoner, two-thirds to another person whose identity was unknown to the N-ALIVE trial.

No reliable inference about NOR's effectiveness for reducing DRDs in the 12 weeks post-release can be drawn from the early-cessation N-ALIVE pilot Trial: five registered DRDs (four randomized to NOR,

of whom two were released without their pack) were fewer than our a priori null-expectation (9.7), perhaps because the expectation was too high rather than as a reflection of NOR's effectiveness. However, the 15% fatality-rate (95% CI: 6% to 24%) at overdoses which our RPSQ-respondents witnessed, typically within 12 weeks of their N-ALIVE release-date, suggests that our ex-prisoners were present at higher-fatality-risk overdoses than suggested by an evidence-synthesis which gave a 6% fatality-rate (95% CI: 2% to 11%) at witnessed opioid overdoses⁶. Explanations for the higher fatality-rate reported by our recidivists range from chance through assortative mixing of ex-prisoners – who then share the same high DRD-rate post-release - to ex-prisoners' high DRD-risk being due to a higher fatality-rate per overdose (rather than to higher overdose-rate with common fatality-rate per overdose).

The Scottish results,^{14 15} data on cost-effectiveness of naloxone,^{14 28} World Health Organization recommendations on naloxone,⁸ UK's legal change on provision of naloxone²⁹, England's increase in opioid-related DRDs³⁰, and prisoners' support for initiatives like the N-ALIVE pilot trial make it timely for England and others to introduce a funded national naloxone policy; but also to evaluate, as Scotland did. In summer 2016, the National Institute for Health Research issued an evaluation-call for naloxone studies in England. This call could address alternative, licensed non-injectable formulations of naloxone or divert attention from England's failure to fund a naloxone policy: NOR with, or without, take-home naloxone.

Our findings add trial-based evidence to the growing consensus^{15 29} that pre-provision of take-home emergency naloxone can enable life-saving interim measures to prevent overdose deaths, and that the period after prison-release is not only a time of great concentration of such deaths but also of opportunity to prevent this major contribution to the global burden of disease³¹. [3882 words]

Research in context

Evidence before this study

The N-ALIVE pilot trial was the first randomized controlled trial to investigate provision of naloxone-on-release (NOR) to prisoners who have previously injected heroin. The MRC funded the N-ALIVE pilot trial to investigate the feasibility of a fully-powered randomized trial.

Added value of this study

The N-ALIVE pilot trial has shown that it is feasible to conduct a large prison-based randomized controlled trial, with good participation from both prisons and prisoners. The finding that two-thirds of administrations of NOR were to someone unknown to the N-ALIVE pilot trial means that alternative research designs should be considered for preventative interventions against fatal overdose.

Implications of all the available evidence

The N-ALIVE pilot trial has demonstrated the feasibility of recruiting many prisons, and consenting large numbers of prisoners, to take part in randomized evaluations that matter to prisoners. The practicality of NOR has now been demonstrated in two prison systems (by Scotland's National Naloxone Policy and by the N-ALIVE pilot trial) and so prisons, internationally, can deliver NOR.

Scotland's non-randomized before/after policy evaluation demonstrated the effectiveness of NOR and community-based take-home naloxone (jointly) for reducing opioid-related deaths in the 4-weeks after prison-release. Two-thirds of administrations of NOR (Scotland; N-ALIVE) were to someone other than the ex-prisoner for whom NOR was prescribed. The N-ALIVE pilot trial reacted promptly to external data from Scotland and from the trial itself to close the N-ALIVE trial to recruitment.

Between 6 000 and 8 000 drug-induced deaths are reported in Europe every year, with opioids their major cause. The European Monitoring Centre for Drugs and Drug Addiction exhorts member-states that many of these deaths could be prevented by adequate peer intervention using naloxone. Age-related rising numbers of opioid-related DRDs complicate before-after evaluations, as in Scotland.

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Table 1: Feasibility outcomes: summary of prior assumptions and actual findings

Outcome	Prior Assumption	Actual	Comment
Number of Participating Prisons	11 prisons in Scotland 14 prisons in England	16 prisons in England (15 open, 1 closed to recruitment)	Consistent with expectation
Target Participant Accrual	5600 participants Original sample size requirement was up to 10% of 56,000 participants	Target revised down to 2,800 for England due to non-participation of prisons in Scotland and Wales. Feb 2014: Interim target revised to 1500 by Aug 31, 2014 Actual accrual at 31/8/14 was 1392 participants. 1500 participants achieved on 8/10/14. Final accrual at Dec 8th, 2014: 1685 participants	Early cessation, see Figure 3
Consent for randomization by eligible prisoners	75%	Based on screening logs, the consent-rate for randomization among eligible prisoners was 72% (1283/1777); 95% CI: 70% to	Upper 95% confidence limit is just short of our prior

		74%.	expectation
Consent to Returned Prisoner Self Questionnaire (RPSQ)	prior expectation of 75%	Consent to complete the RPSQ was given by 85% of participants (1417/1676); 95% CI: 83% to 86%.	Above expectation
Consent to secondary randomization in the phone-contact ancillary study	prior assumption of 50%	Consent to take part in the phone-contact study was provided by 56% (946/1676); 95% CI: 54% to 59%.	Above expectation
Number of Returned Prisoner Self-Questionnaires (RPSQs)	333 recidivist self-questionnaires expected from 2500 randomized & released participants and so we expected $333/2500 \times 1557 = 207$ RPSQs	218 received from 1557 randomized and released participants	Consistent with expectation
Carriage rate in 1st 4 weeks after release	75%	RPSQ 71% (80/112), 95% CI: 63% to 79%	Consistent with expectation
Someone else present at overdose	80%	Based on RPSQs: 53/205 (26%; 95% CI: 20% to 32%) of recidivists reported having injected when alone, and had done so on a mean of 6/14 days. Hence, 95% CI for	Consistent with expectation

		<p>someone else present is: 68% to 80%.</p> <p>Telephone questionnaire: Heroin use in the past three days was reported by 31/81 (38%) of telephone contacts, 10 of whom had injected when alone (12%; 95% CI: 5% to 20%). If the past 3-day rate is taken as representative of the rate throughout the first 4-weeks, then 95% CI for someone else being present at injector's overdose is 80% to 95%.</p> <p>Both consistent with our prior expectation that some-one else is present at 80% of opiate overdoses.</p> <p>Pooled estimate (based on weights 61% and 39%) is 79%; 95% CI: 75% to 84%.</p>	
Telephone Questionnaire Phone contacts	Based on the (Probability of consent) x (Probability of being randomized to Phone Contact	81 out of 1557 randomized and released participants.	Well below expectation

in the 1st or 2nd fortnight	given consent) x (Probability of contact given randomized to Phone Contact) = $1/8 \times \text{Number randomized \& released (1557)} = 195.$	Poisson 95% CI: 63 to 99	
Drug-related Deaths in 1st 4 weeks and next 8 weeks after release	We expect $1/200 \times 1557 = 7.9$ or 8 DRDs in 1 st 4-weeks after release if NOR is not effective; and a further $1/800 \times 1557 = 1.9$ or 2 DRDs in the next 8 weeks.	2 DRDs in 1 st 4-weeks post-release; a further 3 DRDs in the next 8 weeks were registered with Office for National Statistics by 21 April 2016. 1 st 4-weeks, 95 % CI: 0.2 to 7.2 12-weeks, 95% CI: 1.6 to 11.7	Below expectation for the 1 st 4-weeks.
Non-fatal overdose-related admissions within 12 weeks of release	We assume participants' non-fatal overdose admissions to Accident & Emergency within 12 weeks of index release to be between two and eight times as many as DRDs with 2-3 times as many DRDs being our best estimate, thus we expect 20-30 (but up to 80) non-fatal overdose-related Accident & Emergency admissions.	Awaiting Hospital Episode Statistics data from Health and Social Care Information Centre.	No information

Table 2: Baseline Characteristics for 1557 Participants Randomized and Released by 8th December, 2014

Characteristic	NOR		Control		All	
Age (Mean & s.d.) years	Mean 35 years s.d. 7 years		Mean 35 years s.d. 6 years		Mean 35 years s.d. 7 years	
	N	%	N	%	N	%
Age categories (N, %) years						
18-24	40	5	40	5	80	5
25-34	381	50	385	50	766	50
35-44	290	38	302	39	592	39
45+	47	6	46	6	93	6
Gender (N, %)						
Males	762	98	771	98	1533	98
Females	12	2	12	2	24	2
Treatment for Addiction (at Randomization) (N, %)						
Opiate substitution	496	64	503	64	999	64
Opiate detoxification	163	21	163	21	326	21
Other (eg Naltrexone, no current treatment)	114	15	116	15	230	15
Not recorded	1	<1	1	<1	2	<1
Likely Incarceration Interval (N, %) (Date of randomization-Expected Release Date at randomization)						
Within 28 days	532	69	540	69	1072	69
4-12 weeks	171	22	175	22	346	22
>12weeks	17	2	13	2	30	2
Unknown release date	54	7	55	7	109	7

Table 3: Responses to Returned Prisoner Self Questionnaire

Self-Questionnaire	NOR	Control	Total
Number of Forms Completed	112 (51%)	93 (43%)	205
Time from previous release to completion of questionnaire (days)	Mean 79, Sd. 59 Median 64 IQR 37-108	Mean 85, Sd. 66 Median 64 IQR 39-119	Mean 82, sd. 63 Median 64 IQR 38-108
Told family member/friend about Naloxone	76% (85/112)	NA	NA
Told someone about Naloxone	79% (89/112)	NA	NA
Carriage rate of Naloxone	71% (80/112)	NA	NA
How Often did you carry it?			
All	76% (61/80)		
Most	16% (13/80)	NA	NA
Some	6% (5/80)		
No response	1% (1/80)		
What did you do with the Naloxone?		NA	NA
Saved other	14% (16/112)		
Saved self	5% (5/112)		
Lost it	13% (14/112)		
Had it taken away/stolen	10% (11/112)		
Given it away	7% (8/112)		
Thrown it away	2% (2/112)		
Broke the syringe	2% (2/112)		

No answer given	48% (54/112)		
Heroin use in the <u>first 2 weeks</u> after leaving prison			
(Yes or No)	69% (77/112)	65% (60/93)	67% (137/205)
(Smoke/inject)	66% (74/112) N=74, Mean 9/14 days, sd 5 days	65% (60/93) N=60, Mean 8/14 days, sd 5 days	65% (134/205) N=134, Mean 9/14 days, sd 5 days
(Inject)	58% (65/112) N=65, Mean 9/14 days, sd 5 days	43% (40/93) N=40, Mean 10/14 days, sd 5 days	51% (105/205) N=105, Mean 9/14 days, sd 5 days
(Inject, alone)	23% (26/112) N=25, Mean 6/14 days, sd 5 days	29% (27/93) N=26, Mean 6/14 days, sd 4 days	26% (53/205) N=51, Mean 6/14 days, sd 4 days
Self-overdose <=2 weeks of release			
Overdose*	7% (8/112)	2% (2/93)	5% (10/205)
Someone present	8/8	1/2	9/10
Naloxone given	3/8	2/2	5/10
Taken to hospital	4/8	2/2	6/10
Self-overdose >2 weeks of release			

Overdose	4% (5/112)	6% (6/93)	5% (11/205)
Someone present	3/5	6/6	9/11
Naloxone given	3/5	3/6	6/11
Taken to hospital	4/5	4/6	8/11
Presence at overdose of others <=2 weeks of release			
Present	17% (19/112)	13% (12/93)	15% (31/205)
Naloxone given	10/19	1/12	11/31
Taken to hospital	12/19	8/12	20/31
Survived	17/19	11/12	28/31
Presence at overdose of others >2 weeks of release			
Present	15% (17/112)	15% (13/93)	15% (30/205)
Naloxone given	7/17	2/13	9/30
Taken to hospital	9/17	12/13	21/30
Survived	13/17	11/13	24/30
Naloxone acquisition-rate	4% (5/112)	9% (8/93)	6% (13/205)
chi-square on 1df = 1.46			
p=0.226			
Do you think taking part in N-ALIVE changed your own use of heroin in the first 2 weeks after release?			
No	38% (43/112)	65% (60/93)	50% (103/205)
Safer Heroin Use	54% (60/112)	32% (30/93)	44% (90/205)
Riskier Heroin Use	2% (2/112)	3% (3/93)	2% (5/205)

* Fisher's exact test: p=0.116.

Table 4: Risk Score Comparison, based on answers to RPSQ

Risk Score Comparison (lower score, less risky)	N	Median	Mean	sd	Se(Diff)	Observed Difference (95% CI for Difference)
Random Assignment						
NOR	112	4.00	3.86	3.34	0.48	0.34
Control	93	2.00	3.52	3.43		(-0.59 to 1.27)
Safer behaviour as N-ALIVE participant?						
No change/Unsafe	115	3.00	3.87	3.54	0.47	0.38
Safer	90	4.00	3.49	3.18		(-0.54 to 1.30)
Safer behaviour as N-ALIVE participant? (answers by those assigned to control group)						
No change/Unsafe	63	3.00	4.03	3.50	0.71	1.60*
Safer	30	2.00	2.43	3.07		(0.20 to 3.00)
Safer behaviour as N-ALIVE participant? (answers by those assigned to NOR group)						
No change/Unsafe	52	3.50	3.67	3.61	0.64	-0.35*
Safer	60	4.00	4.02	3.12		(-1.61 to 0.91)
Test for Interaction: Difference in differences* (Control-NOR)=1.94, Se for Difference in differences* (Control-NOR) = 0.98 Hence, 95% CI for Difference in differences* is from 0.008 to 3.876 (p=0.049)						

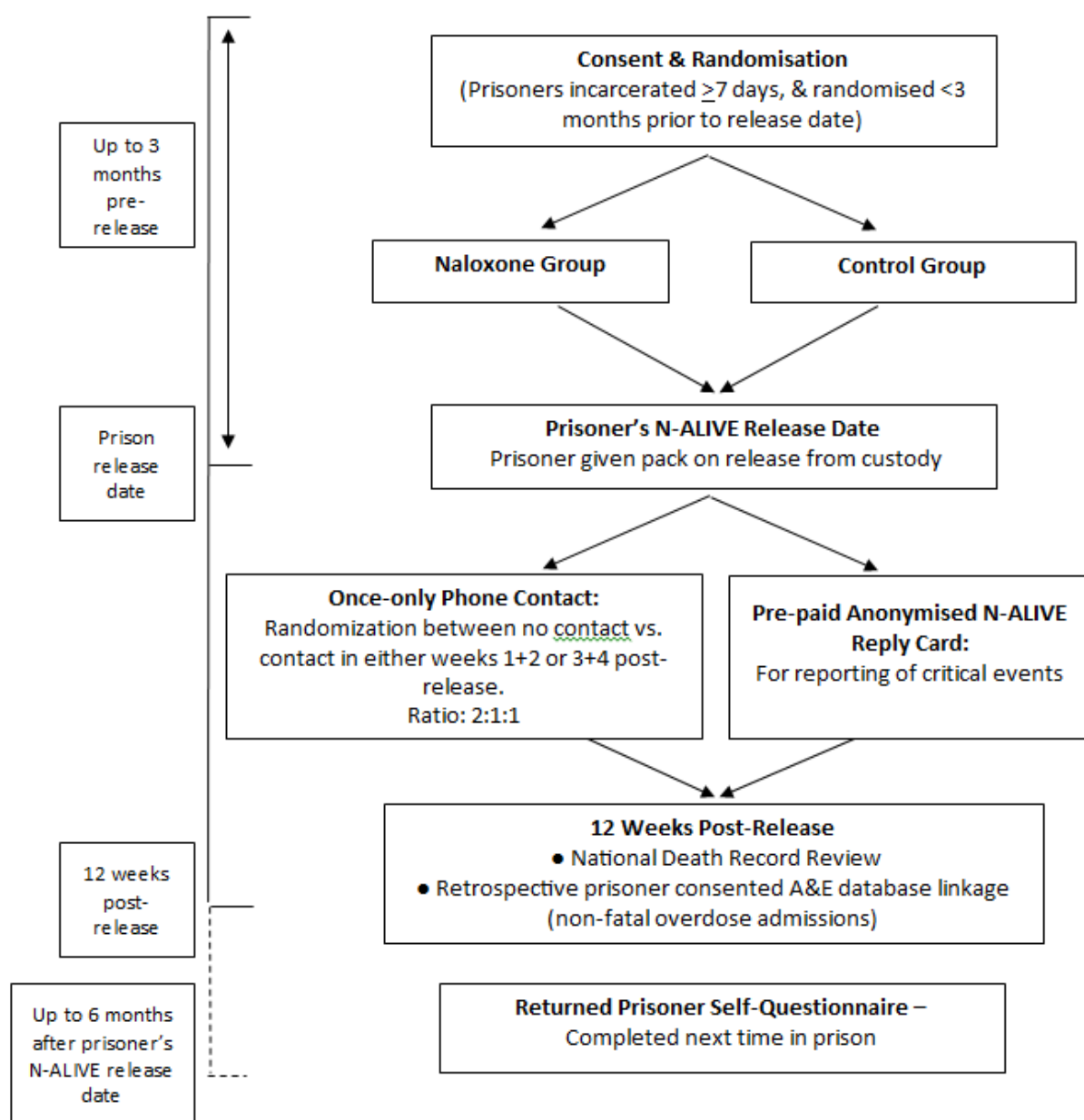


Figure 1: N-ALIVE pilot trial design and outcome measures

A full list of the trial's outcome measures is described in the N-ALIVE protocol, which is available on the N-ALIVE webpage: http://www.ctu.mrc.ac.uk/13391/13399/18277/n-alive_trial_protocol

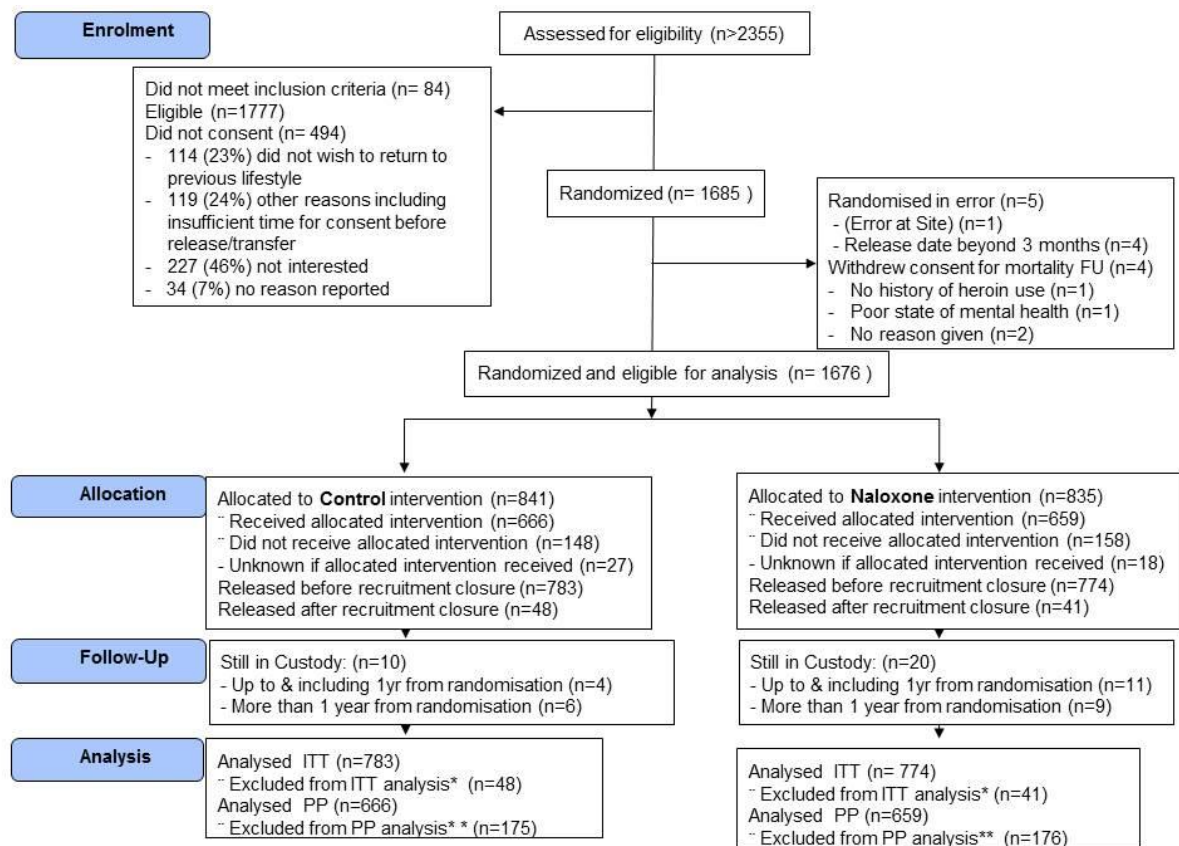


Figure 2: CONSORT Diagram for N-ALIVE pilot Trial

NB. Screening records have been kept only since September 2012 to provide a snapshot of the proportions deemed eligible and subsequently randomized.

* Excluded from Intention-to-Treat (ITT) analysis participants released after recruitment closure (n=48, 40)

** Included in Per-Protocol (PP) analysis participants released with pack only.

As the main trial could not go ahead as planned, it was not appropriate to continue randomizing participants to the N-ALIVE pilot trial. This decision was unanimously agreed by the TS-DMC. This decision was also approved by our appointed Essex 2 Research Ethics Committee.

The finding that Scotland's percentage of opioid-related deaths with a 4-week antecedent of prison-release had decreased from 193/1970 (9.8%) in 2006-2010 to 76/1212 (6.3%) in 2011-2013 ($p < 0.001$) led the TS-DMC to advise that, when randomization to N-ALIVE stopped, all participants who remained in custody be offered naloxone on their release, including those who had been due to receive a control pack.

[illegible]